

111 Amendment  
10/071,490 (60019660-0021)  
Page 10

### REMARKS

Upon entry of this amendment, claims 56-60 and 65-103 will be pending in the above-identified application.

In response to this Office action, claims 1-4, 18, 32, 50, and 61-64 were cancelled. Claims 57, 72 and the specification have been amended herein. Claims 77 - 103 were added. Amendments to the specification were made to conform the pending divisional to the parent application as amended, per the suggestion of the Examiner. Hence, all are fully supported. Amendments and additions to the claims were inserted to a) focus the invention on the important embodiment of compositions and methods for enhancement of bone formation using a mixture of hyaluronic acid, demineralized bone matrix and cancellous bone, and the added feature (set forth in amended claims 72, 73 and new claims 77 - 103) of using a) bone allograft (bone not of the patient) material for the bone-derived components, and/or bone growth materials which consist essentially of the specific ingredients Applicant has selected to mix. These features are clearly not disclosed in the prior art. These will be discussed as pertinent below.

Reconsideration and allowance of all claims are respectfully requested in view of the amendments and the following remarks.

Applicant would like to thank Examiner Fubara for her courteous and helpful interview held with Applicant's representatives on December 1, 2004. During the interview, proposed amendments to the claims, and in particular, withdrawing claims not drawn to compositions or methods focused on the mixture comprising (or even moreso, consisting essentially of, hyaluronic acid, cancellous bone, and demineralized bone matrix with or without a select group of additives (as set forth in claims 56 et seq.) were

111 Amendment  
10/071,490 (60019660-0021)  
Page 11

discussed, along with distinctions of these compositions and mixtures to the cited prior art. Applicant urges that these claims focus on specific embodiments of the invention which are clearly a) not disclosed by such art, b) not suggested by such art, and c) are contrary to both express and implicit teachings of such art. As requested by the Examiner during our recent interview, Applicant provides his detailed explanation of these significant distinctions in the following remarks.

#### The Invention

Prior to Applicant's invention, various compositions were known which are designed to encourage bone growth. However, in spite of the availability of numerous compositions to encourage bone growth, significant needs still exist for additional, effective materials and methods to achieve satisfactory growth of bone to fill bone defects, connect prostheses to existing bone, and fuse fractures and bone grafts to existing bone. In a significant breakthrough, Applicant has devised a novel composition and a method to promote bone formation through stimulation of angiogenesis and osteogenesis using a mixture comprising hyaluronic acid, cancellous bone and demineralized bone matrix. Only utilizing a hindsight reconstruction employing the benefit of Applicant's discoveries can one think to suggest that the invention is either anticipated or obvious over the prior art.

#### Priority Remarks

All amendments entered in the parent application, including those relating to priority statements, pursuant to the Examiner's suggestion, have been entered into the instant divisional. Hence, this issue has been rendered moot.

111 Amendment  
10/071,490 (60019660-0021)  
Page 12

Rejection under 35 U.S.C. § 102(e)

Applicant respectfully traverses the rejection of claims 1, 2, 4, 18, 56, 68, and 69 as being anticipated by Muschler (US 6,049,026), and ask that the rejection be withdrawn. Similarly, the remainder of the pending claims are clearly not anticipated by this reference.

Claims 1, 2, 4, and 18 have been withdrawn without prejudice and the rejection as to those claims is therefore moot. The anticipation rejection is not appropriate for claims 56, 68, and 69, as established below.

To establish anticipation under 35 U.S.C. § 102, the reference must teach every element of the claimed invention either explicitly or impliedly, and any feature that is not directly taught by the reference must be inherently present. MPEP 706.02, Part IV.

The Muschler '026 patent is directed to a method which comprises "collecting a bone marrow aspirate from a donor . . . and passing the bone marrow aspirate suspension through a porous, biocompatible, implantable substrate. . . Preferably, the method is performed intraoperatively using a bone marrow aspirate preferably from the graftee." Col. 3, ll. 23-31. It is clear from the disclosure that Muschler focuses on increasing the number of nucleated progenitor-like cells which are obtained from the bone marrow aspirate. The substrate component serves primarily as a vehicle/carrier for this enriched cell suspension. Cols. 3 - 10. While Muschler mentions hyaluronic acid, cancellous bone and demineralized bone matrix, individually, in a long list of possible materials which could be utilized for the substrate component, he does not mention any possibility of a composition of a mixture of these components for promoting bone growth. Moreover, there is no disclosure, nor suggestion that it would

111 Amendment  
10/071,490 (60019660-0021)  
Page 13

even be suitable, much less beneficial, to select out of the many substrate materials mentioned, a combination of two of the three of hyaluronic acid, cancellous bone, and demineralized bone matrix, much less all three surprisingly found to work as a superior bone formation enhancing unit by Applicant.

In fact, Muschler's disclosure expressly teaches one or the other, not a mix - which he clearly could have said if he deemed such a mixture to be a benefit, or at least an option. Muschler states: "Examples of biocompatible, implantable graft materials having a charged surface include ceramics comprising calcium phosphate such as, for example, hydroxyapatite or tri-calcium phosphate; as well as demineralized bone matrix; or mineralized bone matrix." Hyaluronic acid is not even mentioned individually as a possible substrate material until much later in this discussion. See Col. 4, ll. 1 - 11. Further, while Muschler provides numerous examples of his invention (see Examples 2 - 9), none of these disclose a substrate containing any mixture of substrate materials, much less the specific mixture of hyaluronic acid, demineralized bone matrix and cancellous bone demonstrated by Applicant to enhance bone formation. Hence, Muschler, if anything, teaches away from Applicant's invention.

Not only is there a complete absence of disclosure or suggestion of making such a mixture, or of any benefit in doing so, one skilled in the art would know that in the normal course, there is significant dis-incentive - e.g., of increased cost, of increased labor, of uncertainty of results in risking the interaction - in proceeding to make such a mixture for the substrate without any disclosure/suggestion by Muschler of a benefit for doing so.

111 Amendment  
10/071,490 (60019660-0021)  
Page 14

In contrast, the present invention, as embodied in claims 56, 68 and 69, and all other pending claims, relates to a composition for promoting the growth and strengthening of bone comprising a **beneficial mixture** of hyaluronic acid, cancellous bone, and demineralized bone matrix. This mixture allows for the composition to be thinner so it can flow through an apparatus into the bone with more efficiency. (See Spec. p. 24, lines 6-7). Muschler fails to describe the possibility of having a composition comprising a mixture of hyaluronic acid, cancellous bone and demineralized bone matrix. Thus, Muschler fails to teach not only every aspect of the claimed invention explicitly or impliedly, but its basic focus, and the anticipation rejection must fail.

Accordingly, Applicant respectfully requests withdrawal of this rejection.

#### Rejections under 35 U.S.C. §103

Claims 1-4, 18, 32 and 50 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,017,940 (Petrie et al.) and U.S. Patent No. 5,629,287 (Brown et al.).

As claims 1-4, 18, 32 and 50 all have been canceled without prejudice, this rejection is moot. Applicant respectfully requests withdrawal of this rejection as to those claims.

Claims 3, 32, 50, 57-60, 65-67 and 70-75 were rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,049,026 (Muschler) in view of what is described as "Applicant's admitted prior art".

As claims 3, 32, and 50 have been canceled without prejudice, this rejection is moot as to those claims. Moreover, as explained below (and above), the primary

111 Amendment  
10/071,490 (60019660-0021)  
Page 15

reference, Muschler, is not directed at and is essentially incompatible with the claimed invention. For the following reasons, Applicant respectfully submits that the present invention is not obvious under 35 U.S.C. § 103(a) and requests reconsideration and withdrawal of the §103(a) rejection. Applicant respectfully traverses this rejection.

### **Legal Standards for Obviousness**

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation in the art to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on Applicant's disclosure. See *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

### **The References**

As detailed above, the primary reference, Muschler, a) does not disclose using a mixture of hyaluronic acid, cancellous bone and demineralized bone matrix, b) expressly teaches to use one component or the other - (and implicitly suggests that a combination would be at best unnecessary, and more reasonably, wasteful and risky), and c) only lists these ingredients individually as among that multitude of materials Muschler believed could serve as inert substrate vehicles (for the nucleated cell-containing bone marrow suspension important for bone growth). Moreover, and as discussed with the Examiner, clearly there is no suggestion in Muschler regarding a "method" of bone formation which would employ Applicant's mixture of hyaluronic acid,

111 Amendment  
10/071,490 (60019660-0021)  
Page 16

cancellous bone, and demineralized bone matrix. Finally, Muschler expressly teaches away from using bone allografts as embodied in new claims 77 -90. See Muschler, Col. 3, ll. 28 - 31; col. 10, ll. 48 - 51.

Based on p. 4 of the Office action, it seems certain that the Examiner's citation to "applicants admitted prior art" is to assert that claim 1 equates chitosan with hyaluronic acid (in context), to supply an element missing in Muschler (use of chitosan) present in some claims, since she goes on to state that "the composition of Muschler does not contain chitosan or derivatives thereof." While not acquiescing in the Examiner's conclusions, in view of the fact that any reference to a chitosan component has been removed by amendment from the pending claims, Applicant urges that this argument is now moot. If there is some further basis for which the Examiner relies on "applicants admitted prior art", applicant urges that such has not clearly been set forth in the Office action, and would ask the Examiner to entertain a further interview as to the possible relevancy and appropriateness for any reliance on Applicant's own disclosure in this context prior to issuing any further Office action.

#### **The Claims at Issue**

Claims 65 - 67 and 70 - 71 (as well as claims 56, 68 and 69 rejected as anticipated by Muschler), as amended, relate to compositions which comprise a mixture of hyaluronic acid, cancellous bone, and demineralized bone matrix. Hence, these claims are clearly not obvious over Muschler for the reasons set forth above. Moreover, since Muschler only would suggest use of these components, albeit individually, as inert substrates, it does not follow that the claim elements setting forth various concentration

111 Amendment  
10/071,490 (60019860-0021)  
Page 17

ranges (claims 65 - 67, 70 - 71, see also concentration ranges for method claims 73, 74) which set forth preferred ranges of mixture components for use in bone formation, would be in any way obvious, or subject to merely ordinary tinkering (contra *In re Aller*), since one skilled in the art aware of Muschler would not even be cognizant of the very purpose for modifying such ranges. Hence, these claims are independently patentable for this reason alone.

Claims 57 - 60 and 72 - 76<sup>1</sup> all relate to methods (of inducing bone formation, of filling a bone defect) which clearly require a suggestion that the mixture has bone growth enhancing qualities. A suggestion that the inert substrate materials listed in Muschler have this quality is something entirely missing from Muschler, and hence, there is no basis to find that such method claims are obvious in view of Muschler, separate and apart from the considerations discussed above, as to the claims relating to the mixture composition claims. Again, this rejection as to the method claims, as amended, should be withdrawn.

Finally, amended claims 72, 73 and newly added claims 77 - 90 all relate to compositions and methods utilizing a mixture comprising hyaluronic acid, cancellous bone, and demineralized bone matrix wherein any bone-derived material included in the composition consists essentially of bone allograft material. As Muschler clearly steers toward the use of bone marrow derived from autograft sources, and away from allograft sources, this element provides yet another independent basis for non-obviousness, and these claims should be promptly allowed.



111 Amendment  
10/071,490 (60019660-0021)  
Page 18

Hence, since *prima facie* obviousness requires that there must be a reasonable expectation of success when prior art is modified or combined, and such expectation is entirely absent from the teachings of Muschler as outlined above, the pending rejections under Sec. 103(a) must fall.

Accordingly, the claimed inventions, as herein set forth, are non-obvious under § 103(a). Applicants urge that this rejection be withdrawn.

#### Double Patenting

Claims 54 and 55 were rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 47 and 48 of prior U.S. Patent No. 6,372,257. Claims 54 and 55 have been canceled, which render this rejection moot.

Claims 1-4, 18, 32, 50, 56-60 and 65-76 were rejected under judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-46 of U.S. Patent No. 6,372,257.

Without taking a position as to this issue, if the Examiner declares that, after review of the pending claims as amended, and in view of Applicant's Remarks, that a terminal disclaimer is still appropriate, in order to expedite prosecution, Applicant will forward such a Terminal Disclaimer to render moot this ground rejection.

---

<sup>1</sup> Applicant is not aware of any rejection which specifically embraces claim 76. Hence, it is presumably independently allowable. However, Applicant is proceeding as if claim 76 should be included in this rejection.

111 Amendment  
10/071,490 (60019660-0021)  
Page 19

Claim Objection

Claim 57 was objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only.

In response, claim 57 has been amended to depend from claim 56 only.

Applicant respectfully submits that the objection has been overcome and requests that it be withdrawn.

111 Amendment  
10/071,490 (60019660-0021)  
Page 20

### CONCLUSION


In view of the foregoing, Applicant submits that the pending claims, 56-60 and 65-103, are patentable over the references cited by the Examiner. The newly added claims provide even additional bases for distinguishing the prior art. Further, Applicant has addressed all of the Examiner's rejections and objections. Applicant respectfully requests withdrawal of the rejections and the objections and believes that the claims as presented are now in condition for allowance.

Applicant does not believe that any fees are due for this submission. However, any applicable fees determined to be due can be charged to Deposit Account No. 19-3140.

If the Examiner believes that there is any issue which remains to be resolved, the Examiner is respectfully requested to contact the undersigned attorney at the telephone number listed below.

Dated: 2-1-05

Respectfully submitted,

  
G. Harley Blosser  
Customer No. 26263  
314.259.5200

Submitted Via Facsimile to  
Examiner Fubara 571-273-0594

23156443\V-12